



NOTES

MITOCHONDRIAL DISEASE

GENERALLY, WHAT IS IT?

PATHOLOGY & CAUSES

- Impaired mitochondrial activity → disorder

CAUSES

- Nuclear, mitochondrial DNA mutations

SIGNS & SYMPTOMS

- Muscle weakness, visual/hearing problems, neurological signs/symptoms, heart, kidney, respiratory disorders

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Brain lesions

LAB RESULTS

- Molecular genetic testing
 - Southern blot (deletions/duplications)
 - Sequencing
 - Polymerase chain reaction (PCR)
- Serum tests
- ↑ levels metabolites made by shunt pathways

TREATMENT

MEDICATION

- Enzyme stimulation

OTHER INTERVENTIONS

- Supplementation
- Diet

MITOCHONDRIAL MYOPATHY

osms.it/mitochondrial-myopathy

PATHOLOGY & CAUSES

- Mitochondrial disorders
 - Inability to produce ATP
- Muscles and brain: require high levels of ATP
 - *Only muscles*: myopathy
 - *Muscles, brain*: encephalomyopathy
- Variable clinical phenotypes with myopathy as main/minor feature; phenotypes can overlap

Isolated myopathy

- Nuclear DNA mutations
 - Respiratory chain defects, coenzyme Q₁₀ deficiency
- Rarely caused by mtDNA mutations

Chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome

- Autosomal dominant/autosomal recessive/maternal inheritance
- Nuclear DNA, mtDNA mutations can cause same clinical presentation

VISIT...

LANZAROTE
Caliente.COM

Encephalomyopathy

- Infants, children

Myopathy with diseases of multiple systems

- Barth's syndrome
 - X-linked inheritance; TAZ gene mutation; associated with cardiomyopathy, muscle weakness, neutropenia
- Myoclonic epilepsy with **ragged red fibers** (MERRF)
 - mtDNA mutation → maternally inherited
- Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (**MELAS**)
 - mtDNA mutation → maternally inherited

CAUSES

- Nuclear/mitochondrial DNA (mtDNA) mutation

RISK FACTORS

- Mitochondrial **DNA maternally inherited**; only biological females can pass mutations to children

SIGNS & SYMPTOMS

Isolated myopathy

- Fatigue, myalgia, chronic progressive extraocular ophthalmoplegia (CPEO), progressive extraocular muscles paresis, bilateral ptosis

Kearns-Sayre syndrome

- Chronic progressive extraocular ophthalmoplegia
- Retinal pigment degeneration
- Onset < 20 years old

Encephalomyopathy in infants, children

- Hypotonia, respiratory muscle weakness, poor feeding, seizures

Barth's syndrome

- Underdeveloped, weak muscles; delayed growth; MERRF
- Myoclonus (visible muscle spasms)
- Neurological defects
- Usually begins after normal early development

MELAS

- Stroke-like episodes
- Lactic acidosis
- Hearing, weight loss

DIAGNOSIS

DIAGNOSTIC IMAGING

MRI

- Lesion within deep gray matter in both hemispheres, cerebrum/cerebellum atrophy, lesions similar to stroke

LAB RESULTS

- Serum
 - ↑ lactate and pyruvate, ↑ alanine, ↑ creatine kinase
- Urine analysis
 - Tests for organic acids (↑ Krebs cycle intermediates)
 - Myoglobinuria (in isolated myopathy)
- **Muscle biopsy**
 - Mitochondrial buildup in subsarcolemmal area of affected muscle → **ragged red fibers**
- Histochemical studies
 - **Gomori trichrome stain**: ragged red fibers
 - **Succinate dehydrogenase**: ragged blue fibers
- Biochemical analysis
 - ↓ respiratory chain complex function

OTHER DIAGNOSTICS

Electromyography (EMG)

- Short-lasting, polyphasic motor unit potentials

TREATMENT

OTHER INTERVENTIONS

- Aerobic exercises
- Coenzyme Q₁₀, L-carnitine, creatine supplementation
- MELAS
 - Intravenous arginine hydrochloride with saline, fluids with dextrose
- Avoid
 - Valproic acid, tetracyclines, barbiturates, chloramphenicol, aminoglycosides, metmorfin

PYRUVATE DEHYDROGENASE DEFICIENCY

osms.it/PDH-deficiency

PATHOLOGY & CAUSES

- X-linked disease characterized by abnormal pyruvate metabolism

CAUSES

- E1 alpha gene mutation
 - Pyruvate dehydrogenase E1 alpha subunit deficiency → ↓ production of acetyl-coenzyme A (CoA) → limited citrate production → citric acid cycle (Krebs cycle) impairment
- Impaired Krebs cycle
 - Energy production disorder; brain needs energy from Krebs cycle → neurological symptoms
 - Pyruvate accumulation → transformation to lactate, alanine → lactate buildup → lactic acidosis → metabolic symptoms
- Residual activity of enzyme determines clinical presentation
 - Severe deficiency → congenital brain malformations

- Moderate deficiency → neurological symptoms onset in infancy/late childhood

COMPLICATIONS

- Intellectual disability, microcephaly, blindness
- Leigh syndrome
 - Gray matter degeneration, capillary proliferation, focal necrosis

SIGNS & SYMPTOMS

- Metabolic disorders
 - Lethargy, poor feeding, mental/psychomotor delay
- Neurological symptoms
 - Ataxia, hypotonia, progressive encephalopathy, abnormal eye movements, seizures, dystonia
- Acidosis respiratory symptoms
 - Dyspnea, Cheyne–Stokes breathing, respiratory failure

DIAGNOSIS

DIAGNOSTIC IMAGING

Magnetic resonance spectroscopy

- ↑ lactate levels

MRI

- Cerebral atrophy
- Corpus callosum absence
- Medullary pyramids absence

LAB RESULTS

- Pyruvic acid test
 - ↑ lactate, pyruvate levels in blood, cerebrospinal fluid
- Serum, urine analysis
 - ↑ alanine in serum, urine

TREATMENT

OTHER INTERVENTIONS

- Thiamine, carnitine, lipoic acid cofactor supplementation
- Ketogenic diet
 - Controls lactic acidosis
- Dichloroacetate
 - Stimulation of pyruvate dehydrogenase